IgG4 and cancer - a mechanism of action for cancer relapse and onset

Class switching and tumor promotion...

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Dec 30, 2022

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As you all know, IgG4 has come onto the hot-seat lately in the context of the mRNA shots. I was prompted this morning after watching Chris Martenson's summary video of Jikkyleaks' new FOI findings to look into the relationship between IgG4 and cancer. Again, cancer statistics in VAERS and from clinical settings are completely atypical since the roll-out of the COVID shots and I have been sounding the alarm on this for over a year.

I refer you all to a paper published in 2016 in Current Allergy and Asthma Reports entitled: "IgG4 Characteristics and Functions in Cancer Immunity". [1]

This paper reveals that not only is there a link between tumor progression and the presence of IgG4 due to class switching, but that this link might even be necessary for tumor promotion and progression.

Let's really do some background on IgG4. It's different from its brother and sister IgG subclasses for a very interesting reason: it can swap out its arms - even it's entire half - if it so feels like! This is called Fab arm exchange. [2] It's Fab! Well, not in the context of cancer. But I will get to that. There is an excellent review article in Frontiers in Immunology that describes a new classification for IgG4 antibodies entitled: "A New Classification System for IgG4 Autoantibodies" [3] that I would be remiss not to reference and even quote in this background. The author did a fantastic job.

She opened her review with this phrase:

> IgG4 autoimmune diseases are characterized by the presence of antigen-specific autoantibodies of the IgG4 subclass and contain well-characterized diseases such as muscle-specific kinase myasthenia gravis, pemphigus, and thrombotic thrombocytopenic purpura.

As a side note: Thrombotic thrombocytopenic purpura, or TTP, is a rare and serious blood disease [4] and similar to one of the 2 adverse event types addressed by the CDC/FDA in MMWR reports at the beginning of the roll-out of these COVID-19 products. The refer to it this similar condition as 'Thrombosis with Thrombocytopenia Syndrome'. On Dec 16, 2021, Isaac See: a member of the Vaccine Safety Team working on the CDC COVID-19 Vaccine Task Force, provided the Advisory Committee on Immunization Practices (ACIP) with information on a clearly defined safety signal originating from VAERS. You can see that presentation here.

On IgG4 class switching and what it means pathologically

IgG4 class switching is associated with chronic exposure to antigen. This particular subclass of antibody can outcompete other antibody species, like IgG1, to subsequently block their effector mechanisms. One of these effector mechanisms imposed by IgG1 is tumor control (or suppression), mediated by antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC). And yes, I do see the irony of the three-letter name. These mechanisms are all ways to keep unwanted cells and material under control.

On ADCC, ADCP and CDC (not the agency)

ADCC involves programmed cell death (apoptosis) of unwanted cells. Yes, cells have self-destruct mechanisms. Nature is so cool. This happens via binding of antibodies to antigens presented on unwanted cells (as tags) for subsequent binding of effector cells, like Natural Killer cells, to induce the signal for self-destruction of the unwanted cell. So the bottom line is, antibodies can mediate the induction of the self-destruct signal in cells if they are 'unwanted'.

ADCP involves consumption of unwanted cells by effector cells. Yes, cells eat other cells. Again, nature is so cool. This happens via binding of antibodies to antigens presented on on unwanted cells (as tags) for subsequent binding of effector cells, like phagocytes (macrophages), to induce signals for phagocytosis (eating) of the unwanted cell.

CDC is a mechanism by which antibodies work together with the complement cascade to remove pathogens and/or control overgrowth of unwanted cells. There are three complement pathways called the classical, alternative and lectin pathways. Complement is a necessary and complex system that involves a cascade of proteins and events to unfold that leads to the formation of a Membrane Attack Complex (MAC). The MAC creates a hole in the membrane of the unwanted cell and makes it leak and die. I always wanted to start a band and call it Membrane Attack Complex. *That's* how nerdy I am. One of the proteins involved as a component of the complement cascade is called C3b and it is essential as an opsonin which is a mediator for phagocytosis or opsonization, so think: ADCP.

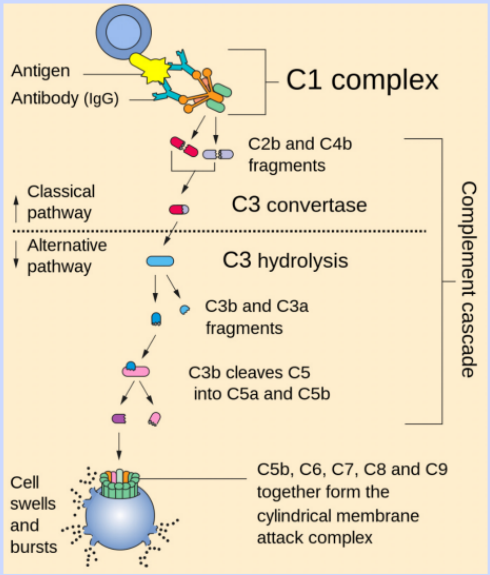

Figure 1: The complement cascade. https://en.wikipedia.org/wiki/Complement_system.

A nice schematic summary of these antibody mechanism of actions can be found in a publication by Ulrike Herbrand in BioProcessing Journal from 2016. [5]

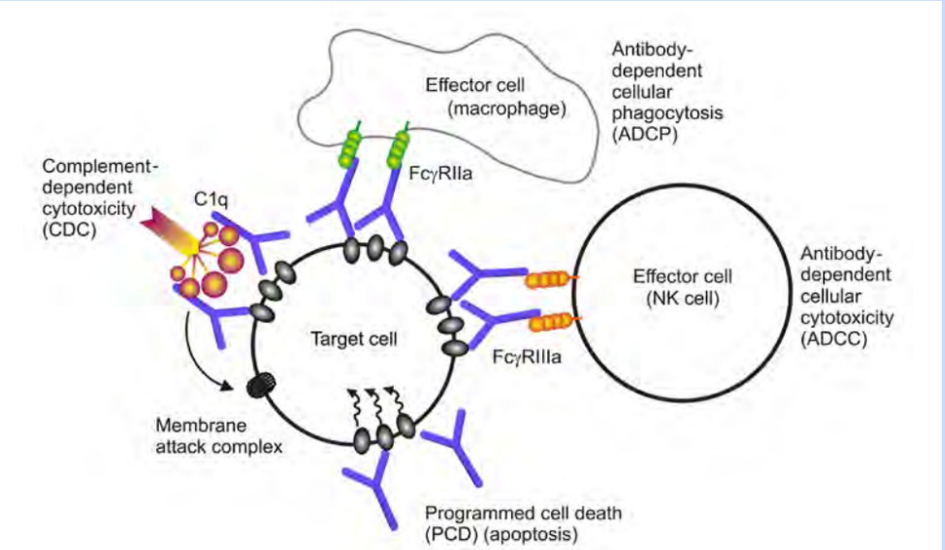

FIGURE 1. Classic functional bioassays designed to assess an antibody's mechanism of action.
(Image courtesy of Charles River Laboratories.)

Figure 2: The mechanisms of action of antibodies.
https://www.criver.com/sites/default/files/resources/Antibody-DependentCellularPhagocytosisTheMechanismofActionThatGetsNoRespect-ADiscussionAboutImprovingBioassayReproducibility.pdf

Now that you understand perfectly how important these antibody functions are for removing unwanted cells and foreign material, you can imagine how important they might be in suppressing tumor formation by suppressing the growth rate of cancer cells. Be very aware, these mechanisms of action are enacted by the **IgG1** subclass. So the question becomes, what happens in the context of cancer, specifically, when the antibody subclass ratio changes due to chronic exposure to antigen? Or more precisely, what happens when the IgG1: IgG4 subclass antibody ratio inverts in the context of tumor suppression?

Here's a schematic from the above-mentioned paper (IgG4 Characteristics and Functions in Cancer Immunity) to illustrate exactly what happens.

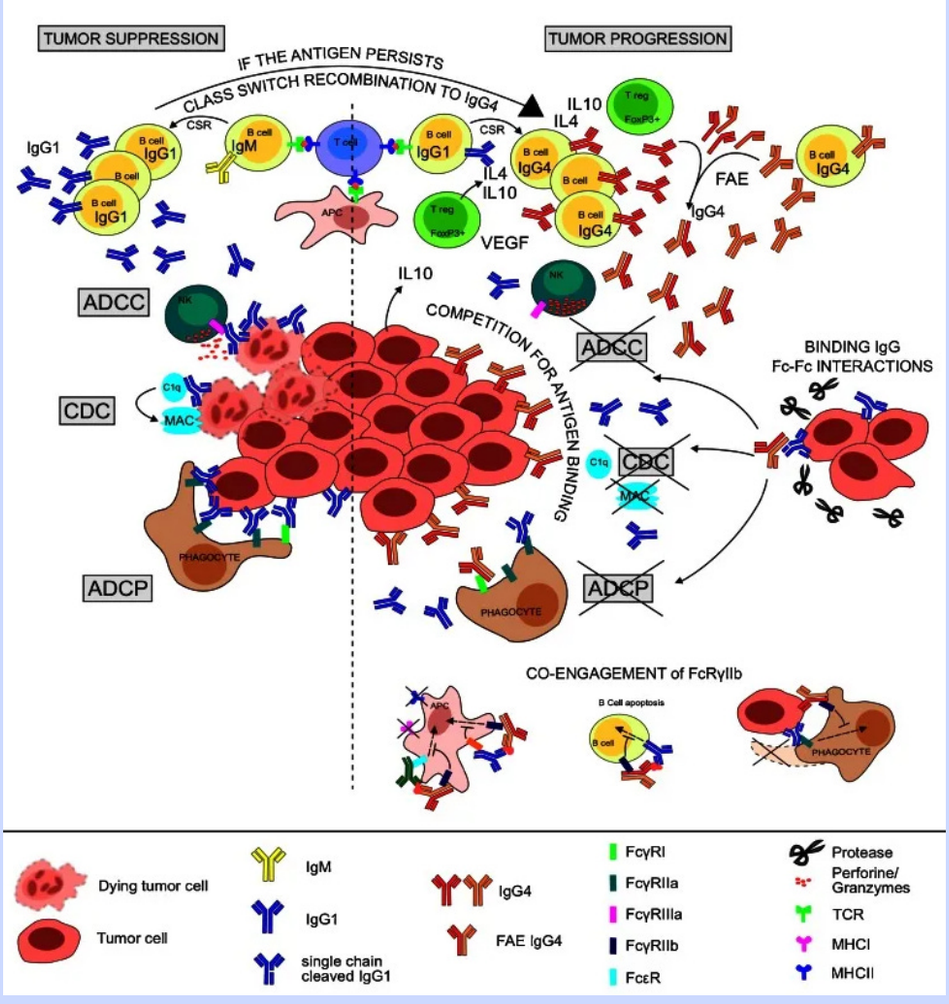

Figure 3: Structural and functional features of IgG4.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4705142/

I want to draw your attention to shift from tumor suppression to tumor progression due to the prevalence of IgG4 as opposed to IgG1. Do you see the problem?

It is very important to understand why the special and unique 'Fab'ulousness of IgG4 is relevant in this context. The authors in this paper write:

> A direct consequence of Fab-arm exchange is the production of IgG4 antibodies with random dual specificity, unable to cross-link identical antigens and therefore perhaps unable to form large [Immune Complex] IC against a specific target.

What this means, is that the unique ability of this typically rare subclass of antibody to switch out its arms, makes it unable to act out the things that I described above that IgG1 can do. Namely, form immune complexes and bind receptors on cells for removal of unwanted cells. So those three ways: the ADCC, ADCP and CDC - that aid in removal of unwanted cells are all nullified in the scenario where IgG4 is prevalent. Worse than that, since the subclass switch is literally the by-product of continuous antigen stimulation, then this is an immunological endorsement of a 'win' for IgG4 if we consider competition for binding sites. In effect, IgG4 outcompetes IgG1 and thus, the scales tip from tumor suppression, to tumor progression. All because of IgG4.

Now I don't want to scare everyone, but persistent re-injection of a messenger RNA that encodes a foreign, highly immunogenic protein, is NOT a good idea in this context. This is *precisely* continuous antigen stimulation by the injectables' contents and their by-products. Not only that, since we know that both the mRNA and the spike protein are long-lasting in the body, you mightn't even have to re-inject yourself repeatedly to qualify as undergoing continuous antigen stimulation. In fact, I would bet that this would be a given. Furthermore, I would bet that due to this continuous antigen stimulation, the IgG1:IgG4 subclass ratio is inverted in people who are persistently making spike and/or re-injecting themselves, and that these people would be subject to cancer promotion, rather than suppression.

My take home message: This is why people are experiencing relapses of cancers previously in remission and this is why new and rare cancers are appearing as well.

1 Crescioli S, Correa I, Karagiannis P, Davies AM, Sutton BJ, Nestle FO, Karagiannis SN. IgG4 Characteristics and Functions in Cancer Immunity. Curr Allergy Asthma Rep. 2016 Jan;16(1):7. doi: 10.1007/s11882-015-0580-7. PMID: 26742760; PMCID: PMC4705142.

2 Schuurman J, Labrijn AF, Parren PW. Fab-arm exchange: what's in a name? MAbs. 2012 Nov-Dec;4(6):636. doi: 10.4161/mabs.22075. Epub 2012 Sep 6. PMID: 22955209; PMCID: PMC3502229.

3 Koneczny I (2018) A New Classification System for IgG4 Autoantibodies. Front. Immunol. 9:97. doi: 10.3389/fimmu.2018.00097.

4 https://rarediseases.org/rare-diseases/thrombotic-thrombocytopenic-purpura/

5 Ulrike Herbrand. Antibody-Dependent Cellular Phagocytosis: The Mechanism of Action That Gets No Respect A Discussion About Improving Bioassay Reproducibility. Spring 2016 BioProcessing Journal [Vol.15/No.1] 26 Since 2002.

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As a lay person, even I can understand your explanation. It's fascinating to me how there are so MANY (seemingly countless) mechanisms of human destruction in this injection.

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Oh.

Bad news then.

Again.

Thanks Jessica for making this accessible and digestible/

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This is one of the emails I received the other day. I get hundreds daily, and I am hearing you all.

This particular note spoke loudly to me and this lovely person gave me permission to share her words.

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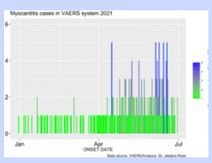

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